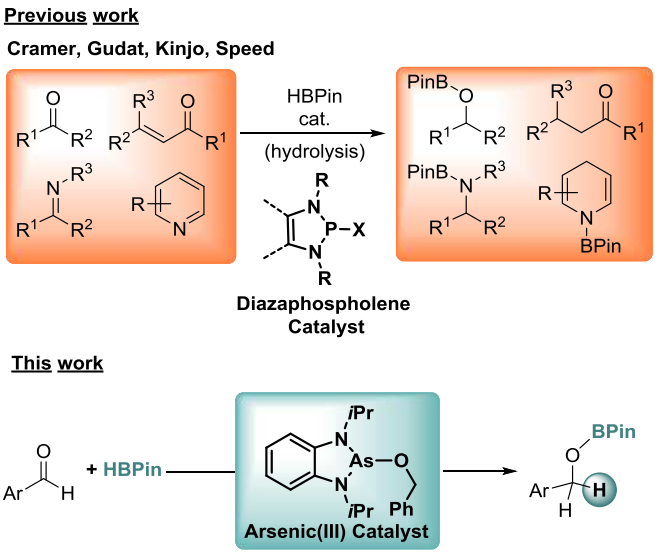
Arsenic Catalysis: Hydroboration of Aldehydes Using a Benzo-fused Diaza-benzyloxy-arsole

Darren M. C. Ould and Rebecca L. Melen*

Abstract: The first example of a homogenous As(III) catalyst for hydroboration has been established. The reaction of *N,N'*-diisopropylbenzene diamine or toluene-3,4-dithiol with $AsCl_3$ yielded the chloroarsoles (**1** and **2**) which upon reaction with benzyl alcohol yielded the benzyloxy benzo-1,3,2-diazaarsole (**3**) and benzo-1,3,2-dithiaarsole (**4**) respectively. **3** was found to be an excellent catalyst for the hydroboration of aldehyde substrates.

In recent years, the chemistry of N-heterocyclic carbene (NHC) analogues in which the divalent carbon atom is substituted by a main group element has garnered attention.[1] Research in this direction has been inspired by both fundamental insight into structure and bonding and well as the applications of such systems in catalysis.[1] In particular, the chemistry of phosphorus (III) heterocycles has received consideration due to their ability to act as hydride transfer reagents in reduction reactions both stoichiometrically[2] and catalytically.[3,4] In this regard, Gudat revealed that secondary 1,3,2-diazaphospholenes or N-heterocyclic phosphanes (NHP-H) have hydridic character and were found to undergo both stoichiometric 1,2- and 1,4-reduction reactions of unsaturated substrates.[2] The catalytic 1,2-hydroboration of carbonyls[3] and imines[4] as well as the catalytic 1,4-hydroboration of α,β-unsaturated carbonyl derivatives[4] were then subsequently established by Kinjo and Speed. In the later part of 2017 and 2018, interest in this area led to the rapid development of chiral-diazaphospholenes for the asymmetric variant of 1,2- and 1,4-reduction reactions by Speed[5] and Cramer[6] respectively. In addition, diazaphospholenes have also been shown to be active in the reduction of pyridines[7] and in other transformations including the transfer hydrogenation using NH_3BH_3[8] as well as hydrosilylation of CO_2.[9] Unlike their phosphorus counterparts, the drive to develop main group catalytic systems based upon the heavier pnictogen, arsenic, has received little attention and the catalytic activity of As(III) heterocycles has not been explored.

The hydroboration of unsaturated systems has widespread applications in the synthetic laboratory and in the chemical industry.[10] With carbonyl or imine functionalities, hydroboration followed by hydrolysis provides access to alcohols or amines respectively, while the reduction of C-C multiple bonds yields borylated molecules for applications in cross-coupling reactions. Although the hydroboration reaction has been rigorously explored using transition metal catalysts,[11] metal-free alternatives are seldom reported.[10] However, the use of metal-free hydroboration catalysts such as those derived from diazaphospholenes or borane Lewis acids has gathered momentum.[2-4,6,12]



Scheme 1. Previous work using diazaphospholene catalysts for hydroboration (top) and this work (bottom).

In our previous work, we have been interested in the structural, photophysical and electronic properties of arsenic heterocycles.[13] Herein, we report the synthesis of novel arsenic heterocyclic compounds and use these as pre-catalysts in the first example of the homogeneous arsole catalysis in the hydroboration of aldehydes with pinacolborane (HBPin).

Initially a series of potential arsenic(III) complexes were prepared from the reactions of *N,N'*-diisopropylbenzene diamine or toluene-3,4-dithiol with $AsCl_3$ to yield the benzo-fused chloro-arsoles (**1** and **2**). Subsequent reaction with benzyl alcohol then yielded the benzo-fused diaza-benzyloxy-arsole (**3**) and benzo-fused dithia-benzyloxy-arsole (**4**) which were both structurally characterized by single crystal X-ray diffraction. Alternately, abstraction of the halide from the chloro-arsoles **1** or **2** with aluminium trichloride and trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded the previously reported cationic arsenium triflate (**5a**) and arsenium tetrachloroaluminates (**5b** and **6**) (Figure 1).[13]

Analysis of the solid-state structures of **3** and **4** revealed that both compounds crystallize in the monoclinic space group $P2_1/c$. For **3** two molecules were present in the asymmetric unit, with metrics of the C_2N_2As ring similar to that previously reported for **1**.[13b] The As–O bond length was found to be 1.82(2) Å, similar to those reported previously for As(III)–O bonds,[14] and an As–O–C interior bond angle of 119.06(12) – 120.79(12)°. With regards to **4**, a similar story was found. One molecule was present in the asymmetric unit and again the metrics of the C_2S_2As ring were similar to that reported for **2**.[14a] For **4** the As–O bond was slightly shorter than in **3**, at 1.789(2) Å, with an As–O–C interior bond angle of 123.1(2)°.

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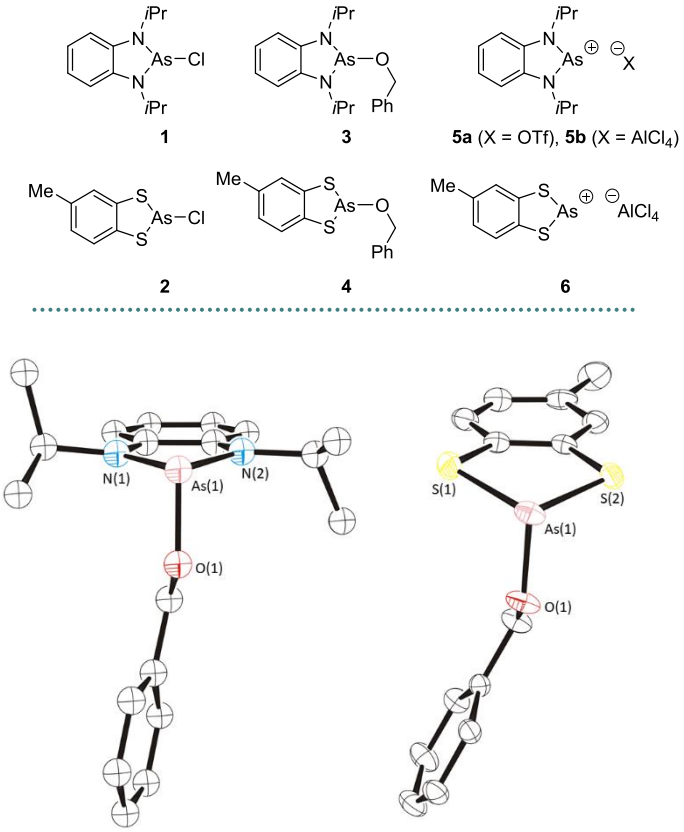
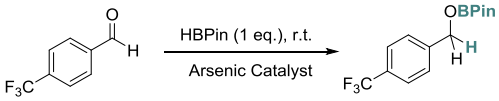


Figure 1. Top: arsoles **1**–**4** and arsenium cations **5** and **6**. Bottom: solid-state structures of **3** (left) and **4** (right). Thermal ellipsoids drawn at 50% probability and H-atoms omitted for clarity.

With this range of arsole and arsenium compounds to hand, we then tested the potential of these species as catalysts for the hydroboration of aldehydes using 4-(trifluoromethyl)benzaldehyde as the test substrate, as this allowed for the reaction conversion to be easily monitored using ^{19}F NMR spectroscopy. Using 10 mol% of the catalyst, the chloride precursors **1** and **2** showed poor activity, giving only 49% and 38% conversion respectively after 24 h (Table 1, entries 1 and 2). The benzyloxy substituted arsoles **3** and **4** on the other hand showed remarkably improved activity, affording quantitative conversion after just 30 minutes in the case of the benzo-fused diaza-benzyloxy-arsole (**3**) and 64% conversion after 12 h for the benzo-fused dithia-benzyloxy-arsole (**4**) (Table 1, entries 3 and 4). Contrary to this, using 10 mol% of the arsenium cations **5a** and **5b** proved less effective, despite using a variety of solvents (Table 1, entries 6–12). For **5a** the highest product conversion was 50% when using CH_2Cl_2, whereas for **5b** just 28% conversion was found using C_6D_5Br. For comparison, the arsenium pre-catalyst **6** was synthesized, which proved highly insoluble in most solvents except C_6D_5Br. Nevertheless, quantitative conversion occurred within 12 hours (Table 1, entry 13), a significant increase compared to **5b**. With **3** proving to be the superior pre-catalyst, the catalytic loading was reduced (Table 1, entries 14–16) with no deleterious effect when using 5 mol% of the catalyst. Further reduction of the catalyst loading to 2 mol% or 1 mol% showed a decrease in activity with 78% and 51% of the reduced product being formed after 12 h respectively. Following this, solvent effects were examined using both coordinating and non-coordinating solvents. Toluene, CH_2Cl_2, $CHCl_3$, Et_2O, CD_3CN and C_6D_6 (Table 1, entries 14 and 17–21 respectively) showed comparable results giving quantitative conversions in under 30 minutes, whereas THF and C_6D_5Br had a detrimental effect upon the reaction (Table 1, entries 22 and 23 respectively). Although a wide range of solvents were found to give quantitative yields for the reaction, for the purposes of evaluating the scope, C_6D_6 was used as the solvent of choice.

Table 1. Optimization of reaction conditions.



Entry	Catalyst	Loading (mol%)	Solvent	Time (h)	Conversion (%)[a]
1	**none**	-	Toluene	24	<10
2	**1**	10	Toluene	24	49
3	**2**	10	Toluene	24	38
4	**3**	10	Toluene	0.5	>95
5	**4**	10	Toluene	12	64
6	**5a**	10	Toluene	24	48
7	**5a**	10	CH_2Cl_2	24	50
8	**5a**	10	MeCN	24	10
9	**5a**	10	C_6D_5Br	24	15
10	**5b**	10	CH_2Cl_2	24	27
11	**5b**	10	MeCN	24	19
12	**5b**	10	C_6D_5Br	24	28
13	**6**	10	C_6D_5Br	12	>95
14	**3**	5	Toluene	0.5	>95
15	**3**	2	Toluene	12	78
16	**3**	1	Toluene	12	51
17	**3**	5	CH_2Cl_2	0.5	>95
18	**3**	5	$CHCl_3$	0.5	>95
19	**3**	5	Et_2O	0.5	>95
20	**3**	5	CD_3CN	0.5	>95
21	**3**	5	C_6D_6	0.5	>95
22	**3**	5	THF	6	41
23	**3**	5	C_6D_5Br	6	58

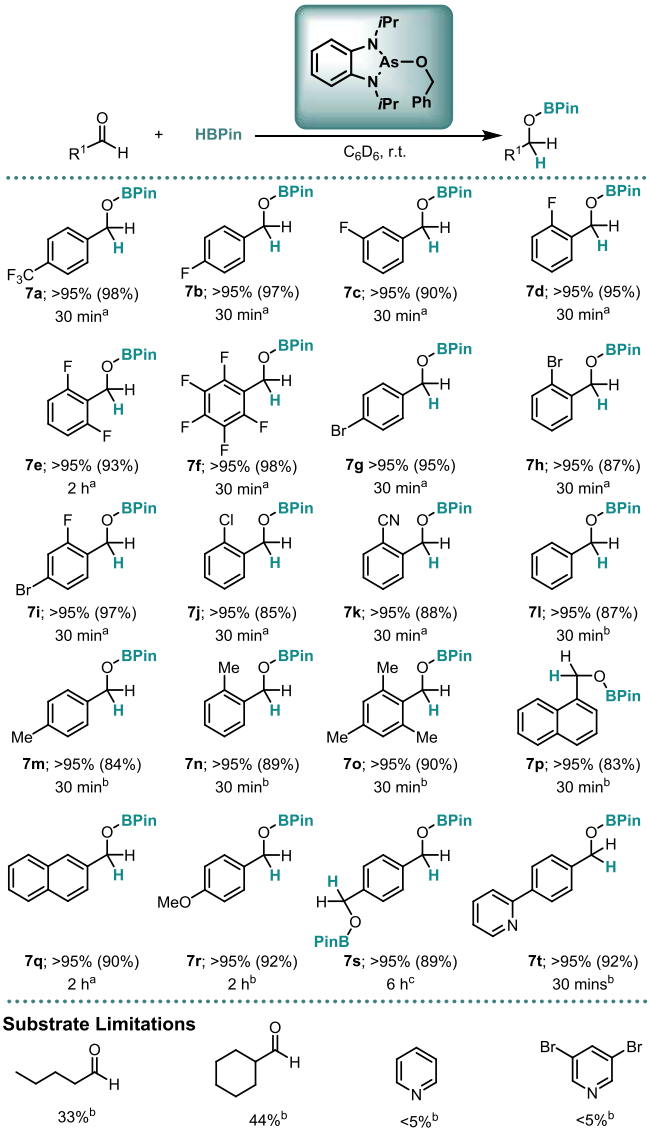
[a] Conversion measured *via in situ* ^{19}F NMR spectroscopy.

Having observed that 4-(trifluoromethyl)benzaldehyde readily underwent hydroboration with HBPin using catalyst **3** under the optimized conditions described above (Table 1, entry 21), the substrate scope was widened to include a variety of aldehydes to test how effective **3** is as a catalyst (Scheme 2). Electron withdrawing benzaldehydes proved very effective for the catalysis, with most substrates undergoing complete conversion within 30 minutes and giving high isolated yields. The fluorinated aldehydes 4-fluorobenzaldehyde, 3-fluorobenzaldehyde and 2-

fluorobenzaldehyde readily converted to **7b–d** respectively within 30 minutes, as detected by both ^{1}H NMR and ^{19}F NMR spectroscopy. In a similar vein, other aldehydes with bromo- or chloro- substituents also worked well yielding **7g–h, 7j** in isolated yields >85%. Likewise, poly-halogenated aldehydes give **7e–f**, **7i** quantitatively with isolated yields >90% although the reaction times for the 2,4-difluorobenzaldehyde took slightly longer (2 h) to reach completion. In addition to using halogenated aldehydes, the electron withdrawing 2-formylbenzonitrile was used, which again gave quantitative conversion to **7k** within 30 minutes and an isolated yield of 88%. Having established the high activity **3** has for benzaldehydes bearing an electron withdrawing moiety, a series of electron neutral and electron donating benzaldehydes was subsequently examined. Benzaldehyde and methyl substituted aldehydes also worked well but needed higher catalytic loadings of 10 mol% to reach completion after just 30 min giving **7l–o**. 1-naphthaldehyde and 2-naphthaldehyde were also successfully converted to **7p** and **7q**. When using 5 mol% of **3**, the 1-naphthaldehyde substrate failed to give quantitative conversion within 24 hours, with ^{1}H NMR spectroscopy showing just 59% conversion occurred. Increasing the catalytic loading to 10 mol% however led to quantitative conversion within 30 minutes to give **7p**. More electron rich aldehydes were also successfully reduced, with 4-methoxybenzaldehyde giving the hydroborated product **7r** in 92% isolated yield after 2h using 10 mol% catalyst. In the case of the bis aldehyde terephthalaldehyde, hydroboration of both aldehyde functionalities was observed when using two equivalents of HBPin, although 20 mol% of catalyst was required and a longer reaction time of 6 h was needed in order to give the product in 89% isolated yield. The use of aliphatic aldehydes was attempted, using pentanal and cyclohexanal. Use of both 5 mol% and 10 mol% of **3** was used in the reduction, however full conversion was not found after 24 hours, with conversions of 33% and 44% being found when using a 10 mol% loading of **3**. In addition, heating these reactions also proved unsuccessful leading to catalyst decomposition.

The recent work of Speed and Kinjo demonstrated the application of phospholene and phosphenium based pre-catalysts in the reduction of pyridines with HBPin.[7] Thus, we probed the arsenic based catalysts in the hydroboration reaction with both pyridine and the more reactive 3,5-dibromopyridine. These showed no reactivity after 24 h using 10 mol% of catalyst **3**. Indeed, when using the pyridyl substituted 4-(2-pyridyl)benzaldehyde, only reduction of the aldehyde was observed giving **7t** in 92% yield after 30 min using 10 mol% of **3**. This demonstrates clear reactivity and selectivity differences between the phosphorus and arsenic based catalysts.

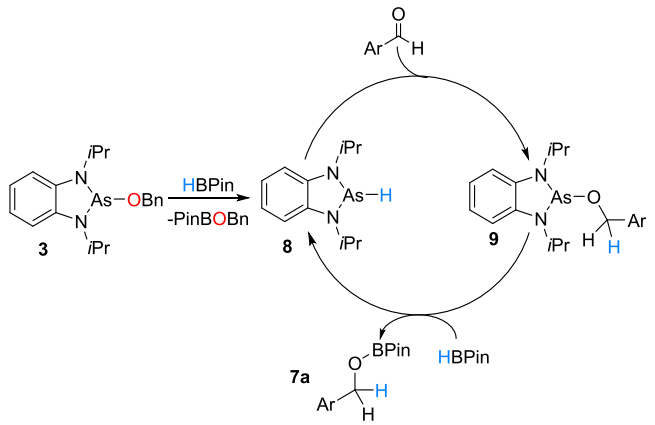
The mechanism for the reaction is proposed to proceed via the pathway depicted in Scheme 3. Mechanistic insight was first obtained through the stoichiometric reaction of pre-catalyst **3** with HBPin, which gave a clear color change from orange to deep red within 5 minutes. The ^{1}H NMR spectrum in C_6D_6 measured after 15 minutes showed a shift for the CH_2 protons on the benzyl group, from 4.03 ppm to 4.77 ppm. Furthermore, analysis of the ^{11}B NMR spectrum revealed a loss of the doublet signal at 28.4 ppm and formation of a new singlet at 22.8 ppm. These observations are consistent with the formation of 2-(benzyloxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (BnO-BPin). Similar by-products were also observed by Speed in the corresponding reaction of the phosphole.[4,5] The other product formed in the reaction was the arsenic hydride species (**8**) which could be detected by HRMS. This species is thought to be the active catalyst for the reaction by analogue to diazaphospholenes where the hydridic nature of the P-H bond prompts catalytic hydroboration of imines.[4,5]



Scheme 2. Hydroboration of aldehydes using benzyloxy-benzo-1,3,2-diazaarsole (**3**). 0.6 ml C_6D_6 solvent, NMR yield calculated from *in situ* ^{1}H NMR spectrum, value in parentheses isolated yield. [a]5 mol% **3**. [b]10 mol% **3**. [c]20 mol% **3**; 2 equiv. HBPin.

Interestingly, the ^{11}B NMR spectrum for the 1:1 stoichiometric reaction of **4** with HBpin reveals a slow reaction, requiring 6 h for complete loss of the doublet resonance corresponding to HBPin. This suggests that the rate of formation of **8** is much faster than that for the sulfur analogue and explains the poorer activity of the benzo-1,3,2-dithiaarsole **4** in the catalytic studies. Further to this, upon the 1:1:1 addition of **3** with HBpin and the aldehyde 4-(trifluoromethyl)benzaldehyde, compound **9** could be detected by

HRMS along with the side-product BnO-BPin further confirming the proposed catalytic cycle.



Scheme 3. Proposed catalytic cycle for the hydroboration of aldehydes with HBPin using the benzo-fused arsole **3** in catalytic quantities.

In this work we have presented the first example of the use of arsenic for homogeneous catalyst for the hydroboration of aldehydes with HBPin. A benzo-fused diaza-benzyloxy-arsole acts as a pre-catalyst and can be employed under mild conditions to give rapid quantitative conversions to the reduced product with most reductions requiring just 30 minutes to reach completion. While the present arsenic species act as precursors for hydroboration catalysis, similar to the analogous phospholene and phosphenium cation-based pre-catalysts, the reduced Lewis acidity provides unique functional group tolerances and alternative selectivities. This provides new insight into the reactivity and main group catalyst design which exploits the reduced Lewis acidity of arsenic. The scope of catalytic reactions that can be performed using homogenous arsenic based catalysts are ongoing within our research group.

Keywords: Arsenic • Hydroboration • Catalysis • Main Group • Boron

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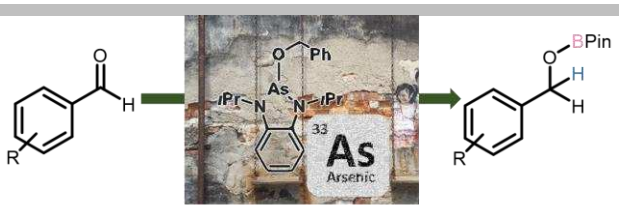
COMMUNICATION

Working with Arsoles: The first examples of homogenous arsenic(III) catalysis has been demonstrated in the hydroboration of a series of unsaturated compounds using benzo-1,3,2-diazaarsoles.



Arsenic based catalyst for the hydroboration of aldehydes

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